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(21) International Application Number: PCT/GB97/01935 (22) International Filing Date: 16 July 1997 (16.07.97) (30) Priority Data: 9614902.6 16 July 1996 (16.07.96) GB		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
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(54) Title: PHARMACEUTICAL COMPOSITION			
(57) Abstract <p>A sustained release rectally administrable, and a delayed and sustained release oral composition is provided wherein the active in diamorphine, morphine, cocaine, theophylline, aminophylline, phenytoin, carbamazepine, phenobarbitone, cyclosporin, diazepam, nitrazepam, temazepam. In a preferred form of these compositions, the active is absorbed predominantly from the colon and provides for reduced peak plasma concentration of active, which otherwise give rise to addiction and other adverse side effects. In some cases, the active is present as a complex in with a carbomer, which provides for enhanced sustained release and therefore more uniform blood plasma concentrations of active.</p>			
<img alt="Mass spectrum plot showing relative abundance (y-axis, 30-70) versus m/z (x-axis, 1000-2000). The plot shows a complex fragmentation pattern with several labeled peaks, including 1171, 1251, 1261, 1263, 1271, 1273, 1281, 1291, 1301, 1311, 1321, 1331, 1341, 1351, 1361, 1371, 1381, 1391, 1401, 1411, 1421, 1431, 1441, 1451, 1461, 1471, 1481, 1491, 1501, 1511, 1521, 1531, 1541, 1551, 1561, 1571, 1581, 1591, 1601, 1611, 1621, 1631, 1641, 1651, 1661, 1671, 1681, 1691, 1701, 1711, 1721, 1731, 1741, 1751, 1761, 1771, 1781, 1791, 1801, 1811, 1821, 1831, 1841, 1851, 1861, 1871, 1881, 1891, 1901, 1911, 1921, 1931, 1941, 1951, 1961, 1971, 1981, 1991, 2001, 2011, 2021, 2031, 2041, 2051, 2061, 2071, 2081, 2091, 2101, 2111, 2121, 2131, 2141, 2151, 2161, 2171, 2181, 2191, 2201, 2211, 2221, 2231, 2241, 2251, 2261, 2271, 2281, 2291, 2301, 2311, 2321, 2331, 2341, 2351, 2361, 2371, 2381, 2391, 2401, 2411, 2421, 2431, 2441, 2451, 2461, 2471, 2481, 2491, 2501, 2511, 2521, 2531, 2541, 2551, 2561, 2571, 2581, 2591, 2601, 2611, 2621, 2631, 2641, 2651, 2661, 2671, 2681, 2691, 2701, 2711, 2721, 2731, 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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/01935

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 248 855 A (BLANK IZHAK ET AL) 3 February 1981 see column 4, line 6-17 - column 5, line 1-9; claims 1,2,5,8 ---	1-6,11, 13
X	CN 1 103 288 A (ZHANG JIE) 7 June 1995 see abstract	1,2
X	& CHEMICAL ABSTRACTS, vol. 123, no. 24, 11 December 1995 Columbus, Ohio, US; abstract no. 322106, ZHANG J.: "Local anesthetic preparations" see abstract ---	1,2
X	EP 0 336 901 A (WARNER LAMBERT CO) 11 October 1989 see claims 12,16 ---	1,2 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

2 March 1998

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/01935

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 354 556 A (SPARKS RANDALL T ET AL) 11 October 1994 see column 3, line 33 - column 5, line 3 ----	1-6,11, 13
X	EP 0 551 626 A (LEK TOVARNA FARMACEVTSKIH) 21 July 1993 see page 8, line 9-10 - page 8, line 45; claims 6,17,20; examples 1-8 ----	1-6,11, 13
X	WO 96 14058 A (EURO CELTIQUE SA ;OSHLACK BENJAMIN (US); CHASIN MARK (US); HUANG H) 17 May 1996 see claim 5; examples 4-13 ----	1-7,11, 13
X	EP 0 636 366 A (EURO CELTIQUE SA) 1 February 1995 see claim 10 ----	1-6,11, 13
X	WO 95 14460 A (EURO CELTIQUE SA ;SACKLER RICHARD (US); GOLDENHEIM PAUL (US); KAIK) 1 June 1995 see claim 16; tables 1-3 ----	1-6,11, 13
X	"Formularium der Nederlands Apothekers" 1980 , KNMP , THE HAGUE XP002056534 see page H4-5 - page H14 ----	3
A	EP 0 672 416 A (EURO CELTIQUE SA) 20 September 1995 see page 2, line 4 -----	1,2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 97/01935

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Subject 1: Claims 1-7, 9, 11, 13
Subject 2: Claims 8, 12
Subject 3: Claims 10

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Claims 1-7, 9, 11, 13

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No	
PCT/GB 97/01935	

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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(54) Title: PHARMACEUTICAL COMPOSITION			
(57) Abstract <p>A sustained release rectally administrable, and a delayed and sustained release oral composition is provided wherein the active in diamorphine, morphine, cocaine, theophylline, aminophylline, phenytoin, carbamazepine, phenobarbitone, cyclosporin, diazepam, nitrazepam, temazepam. In a preferred form of these compositions, the active is absorbed predominantly from the colon and provides for reduced peak plasma concentration of active, which otherwise give rise to addiction and other adverse side effects. In some cases, the active is present as a complex in with a carboromer, which provides for enhanced sustained release and therefore more uniform blood plasma concentrations of active.</p>			

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PHARMACEUTICAL COMPOSITION

The present invention relates to the use of a composition particularly a sustained release composition to 5 limit peak plasma levels of addictive and/or toxic agents.

Addictive agents such as diamorphine and cocaine are rapidly absorbed into the systemic circulation system and as such it is difficult to control the rate of absorption.

10 If the rate of absorption is too high the plasma concentration levels of the agent peaks quickly which can lead to severe adverse side effects and addiction.

Thus the blood plasma concentrations of such drugs has 15 to be strictly controlled, which can be both costly and uncomfortable for the patients. For example diamorphine has to be delivered systemically by subcutaneous or intravenous fusions which is both uncomfortable and often requires hospitalisation.

20 It is therefore an object of the present invention to control the pharmacological profile of toxic and/or addictive agents to provide a beneficial effect while reducing addictive and/or toxic side effects.

25 We have now found a novel delivery system which limits the peak plasma concentrations of toxic and/or addictive agents such as listed below to achieve a more controlled pharmacological profile. This is achieved by delivering a 30 composition for absorption from the intestine, preferably a

sustained release pharmaceutical composition most advantageously for absorption predominantly from the colon.

According to a first aspect of the present invention 5 there is provided a rectally adiministrable and post-gastric delayed release oral (DRO) pharmaceutical composition comprising at least one active selected from diamorphine, morphine, cocaine, theophylline, aminophylline, phenytoin, carbamazepine, phenobarbitone, cyclosporin, 10 diazapam, nitrazepam, temazepam or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

Further aspects of the invention are:

15 (1) the use of at least one active agent as recited in the first aspect in the manufacture of a medicament which is adapted for absorption predominantly from the intestine for the treatment of condition responsive to the active agent; and
20 (2) a method of treatment of a condition responsive to at least one of the active agents recited in the first aspect which comprises administering a composition according to the first aspect of the invention.

25 Dosages and respective uses of the active agents are those given in Martindale, The Extra Pharmacopocia 31st Edition, and The Physicians Desk Reference, 1996 Edition.

30 Typical uses of the aforementioned active agents are as follows: diamorphine (analgesic for the control of moderate to severe pain), morphine (for the control of

moderate to severe pain), cocaine (local anaesthetic), theophylline (asthma, particularly the relief of bronchospasms), aminophylline (acute/ severe asthma).
5 Cyclosporin (auto immune disorders, prophylaxis of graft rejection in organ and tissue transplantation), diazepam (management of severe anxiety disorders and insomnia, for convulsion, particularly status epilepticus and febrile convulsions, as an aid to alcohol withdrawal, and as a premedicament and sedative for surgical procedures and 10 relief of muscle spasm), carbamazepine (epilepsy, neuralgia, and manic depression), phenobarbitone (epilepsy), nitrazepam (insomnia), temazepam (insomnia, premedication for surgical and investigative procedures).

15 By the intestine we mean to include the small and large intestine from the pylorus to the anus.

A preferred form the invention provides the use of a sustained release pharmaceutical composition comprising 20 said pharmacologically active agent to deliver systematically said active agents while limiting peak plasma concentrations, said pharmaceutical composition being delivered for predominant absorption from the large intestine, more preferably the colon.

25 Preferably predominantly at least 70%, more preferably at least 80%, such as at least 85% or at least 90% absorption occurs from the intestine, large intestine or most preferably from the colon.

The inventors have used the absorption profile of the colon to advantage to control the high peak plasma concentrations of addictive and/or toxic agents which are present with other routes of administration. Generally in 5 the alimentary tract food and drugs will pass quickly through the stomach and small intestine but slowly through the colon. Drugs absorbed via the intestine and particular the colon are often metabolised through first pass metabolism in the liver. Drugs are also generally more 10 slowly absorbed from the colon. They have used these apparently negative absorptive features of the intestine and in particular the colon to our advantage in their invention by delivering a composition preferably in sustained release form to the intestine and in particular 15 the colon so that absorption can take place slowly and at a more controlled rate to reduce the high peak plasma concentrations which normally induce the addictive and/or toxic effects of the active agents. For example the inventors say that diamorphine absorbed from the colon, 20 produces much lower peak plasma levels in the systemic blood with a low bioavailability. Therefore a more controlled uniform blood plasma level can be obtained for therapeutic treatment while reducing the adverse side effects induced by high peak plasma levels.

25

By limiting the peak plasma concentration we mean limiting high peak plasma concentrations which are more likely to give rise to addictive or toxic side effect and thereby maintaining a more uniform plasma concentration 30 over a given period of time.

Any active agent which can give rise to addictive and/or toxic side effects if plasma concentrations are too high, can benefit from the invention. Examples of such agents are narcotic analgesics such as diamorphine, 5 morphine, and cocaine; theophylline, aminophylline, phenytoin, carbamazepine, phenobarbitone, cyclosporin, diazepam, nitrazepam, temazepam and pharmacologically acceptable derivatives and metabolites thereof.

10 By pharmacologically acceptable derivatives and metabolites we mean derivatives which exhibit pharmacotherapeutic properties similar to said active agent. This includes pharmacologically acceptable salts, esters and salts of such esters.

15 Pharmaceutically acceptable acid salts are those that form non-toxic acid salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulphate or bisulphate, 20 succinate, maleate, fumarate, bitartrate, gluconate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluene sulphonate, camphorate and pamoate salts.

25 Convenient modes of administration to deliver the compositions of the invention particularly for absorption predominantly from the colon are rectal compositions such as enemas and suppositories, (for colonic absorption) and post-gastric oral compositions such as tablets, capsules, 30 powder or granules. The latter can be adapted to start releasing the active anywhere in the intestine; but

preferably the tablet, capsule or granules will have an outer enteric coating which dissolves in the ileum, more particularly the terminal ileum to allow the active to predominantly be delivered and absorbed in the colon. In 5 this type of composition, some of the active will be absorbed in the ileum because it is released there, but most will be absorbed from the colon.

Typical enema formulations would comprise an effective 10 amount of the drug, for example diamorphine or cocaine, dissolved or dispersed in a suitable aqueous flowable carrier vehicle. The carrier vehicle is preferably thickened with natural or synthetic thickeners such as gums, acrylates or modified celluloses. The formulation 15 can also comprise an effective amount of a lubricant such as a natural or synthetic fat or oil, e.g. a tris-fatty acid glycerate or lecithin. Nontoxic nonionic surfactants can also be included as wetting agents and dispersants. Unit dosages of enema formulations can be administered from 20 prefilled bags or syringes. The carrier vehicle may also comprise an effective amount of a foaming agent such as *n*-butane, propane or *i*-butane. Such formulations can be delivered from a preloaded syringe pressurised container, so that the vehicle is delivered to the colon as a foam, 25 which inhibits its escape from the target site.

A dosage form of active adapted for either rectal or oral delivery may also be complexed with a suspending or thickening agent to prolong release of the dosage form of 30 the active. Such agents include methacrylic acid polymer or acrylic acid polymers, preferably carbomers

(carboxypolymethylene) which are synthetic high molecular weight acrylic acid polymers crosslinked with polyfunctional moieties such as polyallylsucrose.

Generally, carbomers comprise 50% to 70% carboxylic acid groups of the aforementioned active agents. Diamorpine and cocaine form complexes with polyacrylic acid and these form part of the invention. In fact any of the aforementioned active agents which have a basic (e.g. amino or alcohol) group will form complexes in accordance with the invention.

10

Accordingly in a further aspect of the invention there is provided a complex of diamorphine polyacrylate and cocaine -polyacrylate.

15

In a preferred embodiment, an active agent-carbomer complex may be administered rectally as liquid enemas.

Liquid enemas are prepared essentially as described above by forming where possible, an effective amount of an active-carbomer complex in a suitable flowable liquid carrier. The carrier vehicle is preferably thickened with thickeners and can also comprise an effective amount of a lubricant. Unit dosages of enema formulations can be administered from prefilled bags or syringes.

25

The pH of the enema should be 3.0 to 3.5 before a buffering solution is added to raise the pH to between 4.5 to 5.5, ideally about pH 5.0 (at which patients feel comfortable).

30

In a carbomer formulation this can be achieved by adding quantities of a suitable amine protein acceptor to

the preparation. At the same time such a preparation also neutralises some of the carbomer molecules thereby increasing the viscosity. Preferably trometamol is used as a buffering and thickening agent in an enema composition.

5 On average each 100 ml of enema requires about 6 ml (viscosity 4.5 to 7.5 mNm) of a 1% solution of trometamol to give a final acceptable pH of about 5 and viscosity of 3 to 6.5 mNm, ideally 4.0 mNm.

10 When the active agent is administered orally via a DRO tablet, capsule or granules, preferably the dosage form will have an enteric coating which dissolves in the ileum so that the active agent can predominantly be absorbed from the colon.

15 The most extensively used polymer for enteric coating is cellulose acetate phthalate (CAP). However, CAP has an optimum dissolution pH greater than 6, thus early drug release may occur. Another useful polymer is polyvinyl acetate phthalate (PVAP) which is less permeable to moisture and gastric fluid, more stable to hydrolysis and able to dissolve at a lower pH, which could also result in early release of nicotine in the duodenum.

25 Another available polymer is hydroxypropyl methylcellulose phthalate. This has similar stability to PVAP and dissociates in the same pH range. Further examples of currently used polymers are those based on methacrylic acid, e.g., methacrylic acid ester copolymers 30 with acidic ionizable groups, such as Eudragit L and (methacrylic acid copolymer) and mixtures thereof. Dosage

forms coated with Eudragit™, which dissolve in the ileum at about pH 6.8, and in the terminal ileum and caecum at about pH 7.2, have been developed and have been used in the delivery of 5-aminosalicylic acid, and are preferred in accordance with the invention. Methacrylic acid enter copolymer coatings such as Eudragit are preferred to deliver the active for predominant absorption from the colon. Particularly preferred is Eudragit L, most preferably Eudragit LD30.

10

In general coating thickness of about 25 to 200μm, and especially 75 to 150μm, are preferred using about 3 to 25mg, preferably 8 to 15mg of acidic coating material per cm² of tablet or capsule surface. The precise coating thickness will however depend upon the solubility characteristics of the acidic material used and site to be treated.

In a preferred embodiment a capsule is enteric coated and contains a plurality of granules containing the active agent which also are enterically coated. The enteric capsule coating is insoluble in the pH medium of the stomach, but dissolves in the pH of the small intestine, preferably the ileum, to release the enterically coated granules. These coated granules are insoluble in intestinal juice below about pH 7, but are soluble in colonic intestinal juice. The beads have different enteric coated polymers and thickness of coatings to provide a sustained release of the active agent for absorption from the colon. A capsule such as above is described in more

detail in US-A-5,401,512 and WO-A-9214452, the teachings of which are incorporated herein by reference.

In another preferred oral dosage form, the active agent is complexed with a carbomer which is itself coated with an acrylic resin and contained in an enterically coated (preferably Eudragit L) capsules. The capsule coating dissolves in the intestinal juices of the small intestine, preferably the ileum, to deliver the active agent or active agent/carbomer complex to the colon.

A suitable alternative formulation would be to incorporate the active or its salts, and/or the active carbomer complex into heat-meltable amphiphilic excipients such as polyglycolized glycerides of fatty acids such as of the Gelucire™ type (available from Gattefosse, France) or polyoxyethylene glycols, filled into hard gelatine capsules and coated with either cellulose derivative or acrylic polymer enteric coating. Preferred forms of gelucire are 44/14 and 53/10. Both polyacrylic acid complexes and the polyglycolized glyceride excipient release the active slowly over a sustained period and thus further help to reduce high peak plasma levels of active. This is particularly useful when most of the absorption occurs in the colon.

Carbomers are available as fine white powders which disperse in water to form acidic colloidal suspensions (a 1% dispersion has approx. pH 3) of low viscosity. Neutralisation of these suspensions using a base, for example sodium, potassium or ammonium hydroxides, low

molecular weight amines and alkanolamines, results in the formation of clear translucent gels. Cocaine and diamorphine salts form stable water-soluble complexes with carbomers at pH 3.5 and are stabilised at an optimal pH of 5 about 5.6.

In one embodiment of the invention, the carbomer is Carbopol. Such polymers are commercially available from B.F. Goodrich under the designation Carbopol™ 420, 430, 10 475, 488, 493, 910, 934, 934P, 974 and 974P. Carbopols™ are versatile controlled-release polymers, as described by Brock (Pharmacotherapy, 14;430-7(1994)) and Durrani (Pharmaceutical Res. (Supp.) 8;S-135 (1991)), and belong to a family of carbomers which are synthetic, high molecular 15 weight, non-linear polymers of acrylic acid, crosslinked with polyalkenyl polyether. In a particularly preferred embodiment the carbomer is Carbopol™ 974P NF.

To prepare, for example, a diamorphine or cocaine/ 20 carbomer complex the carbomer is suspended in an appropriate solvent, such as water, alcohol or glycerin. Preferably, the carbomer is mixed with water, preferably de-ionised water. Mixtures may range, for example from 0.002 to 0.2 g of carbomer per ml of solvent, preferably from 0.02 to 25 0.1 g of carbomer per ml of solvent. The mixture is stirred thoroughly at room temperature until a colloidal suspension forms. The dispersion may be stirred using a suitable mixer with a blade-type impeller, and the powder sieved into the vortex created by the stirrer using a 500 30 micron brass sieve. This technique allows ample wetting of the powder and prevents the powder from forming a cluster

of particles which then become difficult to wet and disperse.

The cocaine or diamorphine salt may be diluted with 5 any pharmaceutically acceptable organic solvent. In a preferred embodiment, the solvent is an alkanol such as ethanol. Mixtures may range, for example, from 0.01 to 10 g of cocaine or diamorphine per ml of solvent, preferably from 0.5 to 5 g of nicotine per ml solvent. 10 This solution is then added drop wise to the carbomer suspension and mixed continuously until a gel of uniform consistency has formed. Preferably, the cocaine or diamorphine complex is made by combining 1 g said active with from 0.1 to 100 g of carbomer, more preferably with 1 15 to 50 g of carbomer. A gradual thickening of the suspension occurring as neutralisation of the carbomer takes place. The preparation will now take on the appearance of a slightly white translucent gel. This physical change in viscosity and appearance is consistent with neutralisation 20 of the acid by the base.

The gel is then dried. According to one embodiment, the gel is vacuum dried. By way of example, the gel is spread on a glass plate and dried under vacuum at 50°C for 25 about 24 hours. Alternatively, the gel may be freeze-dried. Such methods are well known in the art.

Cocaine or diamorphine carbomer complexes can then be formed into solid dosage forms and a pharmaceutically 30 acceptable coating may be applied, as described above for non-complexed nicotine. For example, the complex may be

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enterically coated thereby delaying the release of the cocaine or diamorphine-carbomer complex until it reaches the ileum and colon.

5 Alternatively the gel can be incorporated into a suitable liquid enema formulation as described earlier.

The invention will be illustrated by way of the following non-limiting examples, and drawings.

10 Figure 1 shows a Fourier Transform Infrared (FTIR) spectrum of a diamorphine-carbomer complex in accordance with the invention; and.

15 Figure 2 shows a FTIR spectrum of a cocaine-carbomer complex in accordance with the invention.

Example 1

20 Method for Making Diamorphine Carbomer Complex
Carbopol 974P (1g. 13.2 mmol carboxylic acid) was stirred into 100ml of deionised water. The resultant colloidal solution was allowed to stand following vigorous mixing for 30 minutes. Meanwhile diamorphine base (50mg) was mixed in 25 absolute ethanol (1ml).

30 5ml (50mg) of the carbomer (Carbopol 974P) colloidal solution was drawn up into a syringe followed by the diamorphine in ethanol solution (1ml). The syringe was shaken thoroughly for a few minutes during which time

14

visual observation noted the formation of a highly viscous clear gel.

This change in physical appearance of the carbomer is
5 consistent with the neutralisation of its carboxylic acid groups in this reaction by the basic unsaturated groups of the diamorphine free base. The gel was spread onto a watchglass to show that it had taken on a clear viscous appearance compared to the semi-opaque white colloidal
10 appearance of the original suspension.

The gel was deep frozen and then freeze-dried. The freeze-dried powder was then triturated to produce a alight fluffy powder slightly off-white in appearance.

15

The weight of powder recovered was 78.9mg. A yield of 78.9%.

Diamorphine/ Carbomer Complex Analyses

20 The chemical composition of the diamorphine carbomer complex was confirmed as follows.

Fourier Transform Infrared (FTIR) pectroscopy

This was performed to analyse the freeze dired diamorphine
25 carbomer complex as well as the starting material, diamorphine base and Carbomer 974P. The absorbencies of these materials were consistent with the presence of a new compound not merely a mixture of the starting materials.

30 The diamorphine - carbomer spectrum is shown as Figure 1.

Ultraviolet (UV) spectrophotometry:

Diamorphine has a distinct absorbance at 279nm in an aqueous acid and 299nm in aqueous alkali medium (1). Standard volumetric aqueous solutions of diamorphine hydrochloride 50mg/ 100ml and 25mg/ 100ml were prepared and their UV spectra determined.

Both solutions gave peak absorbance at 278nm.

10 An aqueous solution of the freeze dried complex (50mg/100ml) was prepared together with acid and alkaline solutions each containing 25mg/ 100ml. The UV spectrum for each solution showed distinct and characteristic peaks at 278nm (aqueous), 276nm (aqueous acid), and 298nm (aqueous alkali).

Thin layer Chromatography:

Thin layer chromatographic plates were prepared by spraying a solution of 1.1M potassium hydroxide in methanol onto 20 plastic silica gel 60 pre-coated sheets with a layer thickness of 200um. When the plate was dry spots of diamorphine free base, carbomer 974P and the diamorphine carbomer complex were prepared by dissolving each powder in absolute ethanol and spotting 50uL on a base line drawn 25mm above the base of the plate.

The dry plate was then placed in the saturated atmosphere of a developing tank which contained a solution of methanol strong ammonia in the ratio 100:1.5 as the mobile phase. 30 The solvent front was allowed to run for 15cm when the plate was withdrawn and dried.

The plate was then sprayed with Marquis Reagent (2) (2ml of formaldehyde 33% m/m plus 100ml of concentrated sulphuric acid).

5

Example 2

Method for Making Cocaine-Carbomer Complex.

Carbopol 974P (1g. 13.2 mmol carboxylic acid) was stirred 10 for 30 minutes into 100ml of deionised water. The resultant colloidal solution was then allowed to stand. Meanwhile cocaine (250mg) was mixed in absolute ethanol (5ml).

15 The 5ml (250mg) cocaine ethanolic suspension was then added to the carbomer (Carbopol 974P) colloidal solution and vigorously stirred. Within a few minutes there was a significant increase in the viscosity of the mixture and visual observation noted the disappearance of the white 20 cocaine suspension with the formation of a viscous clear gel.

This change in physical appearance of the carbomer is consistent with the neutralisation of its carboxylic acid 25 groups in this reaction by the basic unsaturated groups of the cocaine free base. The final gel presentation was clear and viscous compared to the semi-opaque white colloidal appearance of the original suspension.

30 75ml (=940mg of the complex) of the gel was deep frozen followed by freeze-drying. The freeze-dried powder was

then triturated to produce a alight fluffy powder slightly off-white in appearance.

The weight of powder recovered was 894mg. A yield of 95%.

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The remaining 25ml of the gel was used for UV analysis.

Cocaine/ Carbomer Complex Analyses

10 The chemical composition of the cocaine-carbomer complex was confirmed as follows.

Fourier Transform Inframed (FTIR) spectroscopy:
This was performed to analyse the freeze dired cocaine-carbomer complex as well as cocaine base and the carbomer 15 974P. The absorbencies of the complex was consistent with it being a new compound and not merely a mixture of the individual components.

20 The spectrum for the cocaine-carbomer complex is shown in Figure 2.

Ultraviolet (UV) spectrophotometry:
Cocaine has a distinct absorbency at 233nm and 275 in aqueous acid (1). Standard volumetric aqueous acid 25 solutions of cocaine hydrochloride 50mg/100ml, 12.5mg/100ml, 6.25mg/100ml, and 3.125mg/100ml were prepared and their UV spectra determined.

30 Although these solutions gave peak absorbencies at 234 and 275nm but only at the two lower concentration (6.25mg and 3.125mg) were distinct peaks noted at 234nm.

A series of aqueous acid solutions of the freeze dried complex (50mg/100ml to 3.125mg/100ml) were also prepared.

5 Although the UV spectrum for each solution showed peak at and around the expected absorbencies these were inconclusive because of the interference from the background spectrum of the carbomer.

Two volumetric solutions 50mg/100ml and 25mg/100ml were acidified to precipitate our the carbomer and allowed to 10 stand overnight.

The clear supernatant solutions gave more definitive peaks at 234nm.

Thin layer Chromatography:

15 This layer chromatographic plates were prepared by spraying a solution of 0.1M potassium hydroxide in methanol onto plastic silica gel 60 pre-coated sheets with a layer thickness of 200um. When the plate was dry spots of cocaine free base, carbomer 974P and the carbomer-carbomer 20 complex were prepared by dissolving each powder in absolute ethanol and sporting 50uL on a base line drawn 25mm above the base of the plate.

The dry plate was than placed in the saturated atmosphere 25 of a developing tank which contained a solution of methanol/ strong ammonia in the ratio 100:1.5 as the mobile phase. The solvent front was allowed to run for 16cm, when the plate was withdrawn and dried.

30 The plate was then sprayed with Dragendor Reagent (2) (solution (a) 2g bismuth subrute + 25ml glacias acetic

acid+100ml water, (b) 40g potassium iodide + 100ml water). The reagent is then prepared by mixing 10ml of (a), with 10ml of (b), adding 20ml of glacial acetic acid and 100ml of water.

5

Two deep red-orange spots (unfortunately with tailing) indicating the presence of a basic nitrogenous drug were detected both at an Rf value of 65.8 standard reference =65) above the cocaine hydrochloride and the cocaine base 10 baseline spots. The polymer spot was immobile whilst the cocaine in the carbomer complex remained largely confined to the baseline spot although a faint red-orange spot was detectable above its baseline spot also at an Rf value of 65.8.

15

Spot Test:

Identification of the cocaine-carbomer complex was also confirmed by performing a spot test using Dragendorff reagent (2). 20 A deep orange/red colour was observed with the complex whilst the carbomer spot test revealed no colour change. This confirmed the presence of an alkaloidal group. See appendix 5.

25 **Aqueous Solubility:**

The addition of 50mg of the freeze dried cocaine carbomer complex powder to 100ml of deionised water produced a clear solution. This did not happen when 50mg of each of the individual components of the complex were added to the same 30 volume of water. This simple observation clearly indicated that the two water insoluble components of the complex had

20

undegone a chemical reaction forming a water-soluble complex.

1 Clarke's Isolation and Identification of Drugs 1986. The
5 Pharmaceutical Press.

2 Standardised Thin-layer Chromatographic Systems for the
identification of Drugs and Poisons. The Analyst
1982. HMSO.

10 In conclusion, whereas the active agents disclosed
herebefore are rapidly absorbed and give rise to high peak
plasma concentrations, thus leading to intolerable side-
effects including addiction, the inventors surprisingly
found that absorption form the intestine more preferably
15 the large intestine, such as delivery to the terminal ileum
for absorption from the colon, colon (oral and rectal
delivery) or for absorption from the rectum (rectal
delivery) of these highly toxic drugs considerably reduce
the peak plasma concentration and therefore the side-
20 effects.

The invention therefore provides a way in which such active
agents can be used more widely, and more safely for known
therapeutic treatments.

25 When the active agent is delivered in the form of a complex
with polyacrylate, and/or with gelucire, particularly as a
DRO composition, the plasma levels are further limited
thereby further decreasing any remaining side-effects and
30 increasing patient comfort. Furthermore when trometamol is
used as a buffer in an active-carbomer enema there appears

to be some unexplained synergy in that the peak plasma levels and thus side-effects are minimised so that even slightly built patients are not troubled by side-effects.

- 5 All publications, patents and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be
- 10 understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

Claims

1. A complex of diamorphine - polyacrylate and cocaine - polyacrylate.

5

2. A complex as claimed in claim which is a diamorphine - carbomer or cocaine - carbomer complex.

10 3. A rectally adiministrable and post-gastric delayed release oral (DRO) pharmaceutical composition comprising at least one active selected from diamorphine, morphine, cocaine, theophylline, aminophylline, phenytoin, carbamazepine, phenobarbitone, cyclosporin, diazapam, nitrazepam, temazepam or a pharmaceutically acceptable salt 15 thereof together with a pharmaceutically acceptable carrier.

20 4. A rectally administrable or DRO composition as claimed in claim 3 wherein the active agent is in a form of a complex as claimed in claims 1 or 2.

5. A DRO composition as claimed in claim 3 or 4 which releases the active agent in a sustained release manner.

25 6. A DRO composition as claimed in any of claim 3 to 5 which is in the form of a tablet capsule or granules having an outer enteric coating for dissolution in the terminal item to allow said active agent to predominantly be absorbed in the colon.

7. A DRO composition as claimed in claim 6 wherein the enteric coating is Eudragit L.
8. A DRO composition wherein the active agent is 5 incorporate into polyglycolized glyceride excipient.
9. A DRO composition as claimed in claim 7 wherein said excipient is Gelucire.
10. 10. A delayed and sustained release capsule for selectively delivering an active agent to the colon, said capsule comprising as active agent, diamorphine, morphine, cocaine, theophylline, aminophylline, phenytoin, carbamazepine, phenobarbitone, cyclosporin, diazepam, nitrazepam, temazepam, and pharmacologically acceptable derivatives or metabolites thereof, said capsule comprising a plurality of enterically coated granules of active agent adapted to predominantly release the active in a sustained release manner in the colon, said capsule including an outer enteric coating which dissolves in the terminal ileum to release the granules for absorption in the colon.
11. A delayed and sustained release tablet, capsule or granules for oral administration comprising a complex of active agent and carbomer, said active agent being 25 diamorphine, morphine, cocaine, theophylline, aminophylline, phenytoin, carbamazepine, phenobarbitone, cyclosporin, diazepam, nitrazepam, temazepam and pharmacologically acceptable derivatives and metabolites thereof.

12. A delayed and sustained release oral capsule, said capsule comprising an active agent diamorphine, morphine, cocaine, theophylline, aminophylline, phenytoin, carbamazepine, phenobarbitone, cyclosporin, diazepam, 5 nitrazepam, temazepam and pharmaceutically acceptable salts thereof incorporated into a heat meltable polyglyceride fatty acid excipient and encapsulated in the capsule, said capsule having an outer enteric coating which dissolves in the terminal item to release the active for absorption 10 predominantly in the colon.

13. Use of at least one active agent selected from diamorphine, morphine, cocaine, theophylline, aminophylline, phenytoin, carbamazepine, phenobarbitone, 15 cyclosporin, diazepam, nitrazepam, temazepam and pharmaceutically acceptable derivatives and metabolites thereof in the manufacture of a medicament which is adapted for absorption predominantly from the colon for the treatment of conditions responsive to the active agent.

20

14. Use as claimed in claim 12 wherein the medicament is a composition as defined in claims 9 or 11.

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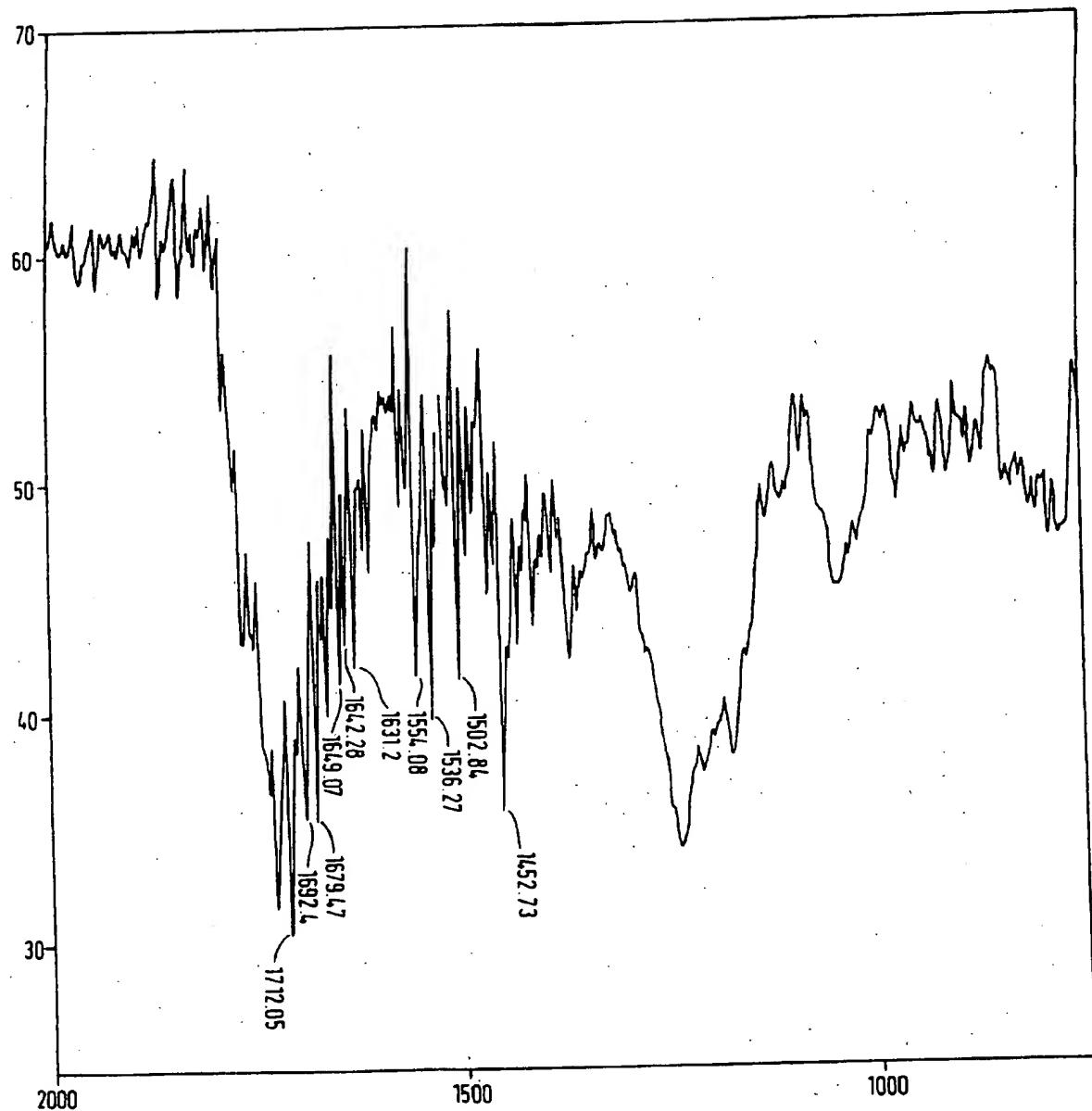


FIG. 1

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